CHAPTER 14

Psychobiological Laboratory Assessment of PTSD

MATTHEW J. FRIEDMAN

During the past 20 years a number of experimental laboratory procedures have been utilized to distinguish individuals with posttraumatic stress disorder (PTSD) from those without the disorder. Such procedures can be divided into baseline assessments and provocative tests. In all cases, research with these various techniques has significantly advanced our understanding of the unique pathophysiology of this disorder. In no case, however, has a research protocol achieved the status of a routine clinical assessment technique. The major reason for this is that PTSD-related abnormalities are generally found within the normal clinical range and, therefore, can be detected only in comparison with non-PTSD control groups. A second reason is that inconsistent findings from one research laboratory to the next, with respect to some measures, have cast doubt on the general utility of such tests at this time. A third reason is that most psychobiological research to date has focused primarily on military veterans and to a lesser extent on women exposed to sexual trauma as adults or children. There have been too few psychobiological observations on survivors of nonmilitary or nonsexual trauma. Furthermore, there have been too few observations on females, children, non-Caucasians, and non-European Americans.

Despite these considerations, I believe that there are many reasons to hope that accurate, inexpensive, and clinically useful laboratory techniques for assessing PTSD will be developed within the foreseeable future. Because other chapters have focused on psychophysiological, neuropsychological, and neuroimaging assessment, I focus in this chapter on laboratory measurement of neurotransmitters, neuropeptides, and neurohormones.

THE HUMAN STRESS RESPONSE AND THE PATHOPHYSIOLOGY OF PTSD

First, it is important to establish a conceptual framework by considering the human stress response. The human stress system has evolved for coping, adaptation, and preservation of the species. It encompasses central and peripheral nervous systems, the endocrine system, and the immunological system. The amygdala plays a key role in coordinating the response to stress or threat through activation of the hypothalamic–pituitary–adrenocortical (HPA) and the locus coeruleus–norepinephrine-sympathetic (LC–NE) systems. Corticotropin releasing factor (CRF) plays a strategic role because it activates not only HPA, LC–NE, and immunological mechanisms but also a complex cascade of reactions involving many other neurotransmitter, neurohormonal, immunological, and metabolic mechanisms, including adrenergic, serotonergic, opioid, glutamatergic, GABA-ergic, cholinergic, and cytokine systems (Chrousos, 1998; McEwen, 1998). (It is important to keep in mind that CRF may also initiate more fine-grained actions involving only the HPA, only the LC–NE, or only other specific immunological or neurobiological systems. In the face of an overwhelming stressor, however, it is not unreasonable to consider CRF from the present standpoint, as the principal neurohormonal mover in the complex spectrum of actions that characterize the human stress response.)

PTSD results when a traumatic experience overwhelms the capacity of an individual's stress system. Failure to cope with the demands of traumatic stress might take a number of forms, such as inability to mobilize an adequate response, inability to achieve normal recovery, and inability to calibrate the magnitude of the stress response to the actual psychobiological demands of the traumatic situation.

From this perspective, PTSD exemplifies the human stress response gone wrong. As a result of the organism's failure to cope and recover, key psychobiological functions are altered. Dysregulation of the HPA, LC–NE and immune systems produces many secondary abnormalities that are mediated through a cascade of downstream mechanisms. In chronic PTSD, a new balance is achieved in the face of such stable psychobiological alterations. Countermeasures are brought into play to compensate for (1) the failure to mount an adequate response; (2) the failure to shut off activated mechanisms in order to achieve normal recovery; (3) the failure to habituate to repeated challenges of the same kind; and (4) the failure to calibrate subsequent stress system responses to realistic demands of the situation (Friedman, 2002; Friedman & McEwen, 2004). McEwen (1998) has called the process of achieving stability in the face of such altered neurobiological mechanisms *allostasis*, whereas the price of achieving such stability in the face of these deleterious functional alterations is called *allostatic load*. As I discuss later, allostatic load in chronic PTSD has already been detected in a number of key systems shown in Table 14.1, such as HPA, LC–NE, serotonergic, opioid, and endocrinological sys-

TABLE 14.1. Biological Abnormalities Associated with PTSD

Neurobiological system	Specific indicator	Abnormality
HPA	CRF	Increased
	ACTH	Variable findings
	Cortisol	Variable findings
	DHEA	Reduced
	DHEA/cortisol	Reduced?
	GR receptors	Supersensitivity?
Adrenergic	Tonic norepinephrine/epinephrine	Increased
	Phasic norepinephrine/epinephrine	Increased
	NPY (tonic and phasic)	Reduced
	Dopamine	Increased
	Galanin	Unknown (possibly reduced)
Serotonin	$5HT_{1A}$ receptor function	Unknown (possibly reduced)
	$5HT_{2A}$ receptor function	Unknown (possibly elevated)
Opioid	Beta-endorphin/enkephalin	Mixed findings generally indicative of systemic dysregulation
Glutamatergic	NMDA, non-NMDA, metabotropic receptors	Unknown
GABA-ergic	$GABA_A$ receptors, benzodiazepine receptors	Unknown (possibly blunted)
Substance P	Substance P	Unknown (possibly blunted)
Thyroid	T_3, T_4, TSH	$\uparrow T_3$, $\uparrow T_4$, $\uparrow T_3/T_4$, $\downarrow$TSH
Gonadal	Testosterone	Mixed results
	Estrogen	Unknown
Growth	GH	Tonic GH unchanged; decreased GH activation by clonidine and levodopa
Immunological	Cell-mediated immunity	Immunosuppression
	Cytokine levels	Increased inflammatory cytokines (IL-1, IL-2, IL-6, TNF)

Note. HPA, hypothalamic–pituitary–adrenocortical; CRF, corticotropin releasing factor; ACTH, adrenocorticotropic hormone; DHEA, dehydropiandosterone; GR, glutocorticoid receptor; 5HT, 5-hydroxytryptamine (serotonin); NMDA, *N*-methyl-D-aspartate; GABA, gamma amino butyric acid; T_3, triiodothyronine; T_4, thyroxine; GH, growth hormone; IL, interleukin; TNF, tissue necrosis factor.

tems. Based on laboratory findings, it is reasonable to expect that allostatic load will also be detected in glutamatergic, GABA-ergic, immunological, and other mechanisms, as well. More information on such abnormalities can be found elsewhere (Friedman, 1999; Friedman, Charney & Deutch, 1995; Charney, 2004; Morgan et al., 2003).

HYPOTHALAMIC–PITUITARY–ADRENOCORTICAL SYSTEM

A large body of evidence indicates that HPA abnormalities figure prominently in the pathophysiology of PTSD. Investigations have focused mostly on CRF release, cortisol levels, and glucocorticoid receptor sensitivity.

Corticotropin Releasing Factor

CRF initiates both the HPA and LC–NE systems, as well as other neurotransmitter, neurohormonal, metabolic, and immunological responses. Studies with male combat veterans and premenopausal survivors of childhood sexual abuse have detected elevated cerebrospinal fluid CRF levels and enhanced hypothalamic release of CRF among people with PTSD compared with those without (Baker et al., 1999; Bremner et al., 1997; Yehuda et al., 1996). Mixed results have been found with respect to the ACTH response to CRF (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Smith et al., 1989).

Cortisol Levels

Findings on urinary free cortisol levels are mixed. Earlier studies with male combat veterans and elderly male and female Holocaust survivors generally found reduced 24-hour urinary cortisol levels in those with PTSD compared with trauma survivors without PTSD. Other studies with male veterans have shown no difference. More recent investigations, mostly with premenopausal women and traumatized children, have found the opposite (i.e., elevated urinary cortisol levels) among those with PTSD (see reviews by Heim et al., 2001; Rasmusson & Friedman, 2002; Rasmusson et al., 2001; Yehuda, 1999).

To complicate the picture even more, the same patient may exhibit remarkable fluctuations in urinary cortisol during a single hospitalization. Mason, Giller, Kosten, and Wahby (1990) measured urinary cortisol levels in hospitalized combat veterans with PTSD at admission, midpoint, and discharge. Many veterans with low urinary cortisol at admission exhibited high levels several weeks later during that phase of the hospitalization that included therapeutic reexposure of patients to stressful traumatic memories of the Vietnam War. After more weeks had passed, these same veterans reexhibited low urinary cortisol prior to discharge. The investigators proposed that baseline

HPA function can fluctuate dramatically in response to external (stressful) circumstances.

Dehydroepiandosterone

In addition to releasing cortisol, ACTH also stimulates the release of dehydroepiandosterone (DHEA) from the adrenal cortex. Both hormones are secreted episodically and synchronously in response to ACTH (Rosenfeld et al., 1971). DHEA antagonizes the actions of cortisol and other glucocorticoids (Browne, Wright, Porter, & Svec, 1992). Rasmusson and associates (Rasmusson et al., in press) suggested that through cortisol antagonism, DHEA release protects against the effects of excessive adrenocortical activation. Morgan (2001), working with military special forces personnel exposed to a severely stressful training exercise, suggested that DHEA/cortisol ratios may represent a useful measure of psychobiological resilience.

Glucocorticoid Receptor Sensitivity

HPA balance is maintained by a negative feedback system. CRF produces ACTH secretion, which promotes cortisol release from the adrenal cortex. The hypothalamus monitors the amount of circulating cortisol through its glucocorticoid receptors. When a sufficient number of these receptors are occupied by cortisol, CRF secretion is inhibited. This negative feedback mechanism prevents blood cortisol levels from getting too high. When cortisol levels are too low, however, and an insufficient number of hypothalamic glucocorticoid receptors are occupied, CRF is released until the proper blood cortisol level is achieved.

An important theory concerning HPA function in PTSD, derived mostly from Yehuda's work (see Yehuda, 1997, 1999), suggests that there is a stable neurohormonal equilibrium marked by low cortisol, an increase in the number (e.g., upregulation) of glucocorticoid receptors, and enhanced negative feedback of the HPA system due to supersensitivity of these same glucocorticoid receptors detected by the dexamethasone suppression test (DST). The paradox of this elegant model is that, despite lower cortisol levels, the system may act as if there were excessive HPA activity because of the supersensitivity of the glucocorticoid receptors. Indeed, many of the research findings presented here are consistent with the hypothesis that HPA activity is elevated, not reduced, in PTSD.

To summarize, HPA function appears to be dysregulated in PTSD, although variable experimental findings make it impossible to specify a unitary pattern of abnormalities at this time. Many findings suggest enhanced HPA activity due to some combination of elevated CRF activity, glucocorticoid receptor sensitivity, and, in some cases, elevated cortisol levels. Reports vary regarding whether hypocortisolism in PTSD is or is not associated with glucocorticoid receptor supersensitivity. Such variability may reflect tonic (e.g., baseline), as well as phasic (e.g., stress-induced episodic), HPA abnormalities, the magnitude of an individual's stress response at the time of measurement, methodological issues regarding the collection and assay of blood or urine samples, and/or gender-related differences in neurohormonal factors affecting CRF, cortisol levels, or glucocorticoid receptor sensitivity.

ADRENERGIC ABNORMALITIES IN PTSD

Because the LC–NE system is activated during the human stress response (Cannon, 1932), it is not surprising that PTSD has been associated with both tonic and phasic alterations of catecholaminergic function.

Tonic Adrenergic Activity

Twenty-four-hour urinary norepinephrine and epinephrine have been measured in male combat veterans, male and female Holocaust survivors, and female sexual abuse victims. Results in many, but not all, studies have shown elevated catecholamine levels among individuals with PTSD compared with both trauma exposed/no-PTSD and nonexposed controls (see Southwick et al., 1999, for references). Elevated CSF norepinephrine levels have also been detected (Geracioti et al., 2001).

It would be expected that increased catecholamine levels would produce a compensatory reduction (or down-regulation) of adrenergic receptors. This effect has been shown in research on both alpha-2 and beta adrenergic receptors. Two studies (with combat veterans and traumatized children, respectively) have shown reduced platelet alpha-2 binding sites among individuals with PTSD compared with controls (Perry, 1994; Perry, Giller, & Southwick, 1987). In addition, there is evidence that beta adrenergic receptors are also down-regulated (Lerer, Gur, Bleich, & Newman, 1994).

Phasic Adrenergic Activity

A variety of challenge studies have consistently demonstrated excessive phasic adrenergic responses among individuals with PTSD. In addition to physiological hyperreactivity, exposure to psychological stressors has been associated with abrupt elevations in plasma epinephrine and norepinephrine, respectively, in two studies with combat veterans with PTSD (Blanchard, Kolb, Prins, Gates, & McCoy, 1991; McFall, Murburg, Ko, & Veith, 1990).

Yohimbine, an alpha-2 adrenergic receptor antagonist, has been an important pharmacological probe in studies on phasic adrenergic activity. Yohimbine enhances adrenergic activity by blocking the inhibitory presynaptic alpha-2 receptor, thereby enhancing presynaptic release of norepinephrine. An investigation with Vietnam combat veterans found that among the participants with PTSD, yohimbine elicited panic attacks, combat-related flashbacks, and elevated brain adrenergic metabolism in contrast to veterans without PTSD, who did not exhibit such abnormalities (Bremner, Innis, et al., 1997; Southwick et al., 1997).

Thus studies on catecholamine function indicate that the major adrenergic abnormality in PTSD is a hyperreactive phasic response, although alterations in tonic activity have also been detected.

Neuropeptide Y

Neuropeptide Y (NPY) is a neuropeptide found in adrenergic neurons that is released along with norepinephrine during intense activation of the adrenergic system by yohimbine or excessive exercise (Pernow, 1988; Rasmusson et al., 2000). It apparently enhances the efficiency of adrenergic transmission in the sympathetic nervous system (Colmers & Bleakman, 1994) and appears to have a profound anxiety-reducing effect (Kask, Rago, & Harro, 1996). Of particular relevance to our previous discussion of HPA function, anxiolytic doses of NPY also antagonize the anxiogenic and other actions of CRF, making NPY a potential major moderator of the intensity of the human stress response (Britton et al., 1997). NPY is, therefore, an important neuropeptide to consider in PTSD because it is released during intense phasic activation of the adrenergic system and because it is a potent antagonist of CRF.

Veterans with PTSD exhibited significantly lower baseline NPY levels, as well as a blunted NPY response to yohimbine, in comparison with non-PTSD controls (Rasmusson et al., 2000). This result is consistent with animal studies showing reduced NPY inhibition of adrenergic function following chronic stress (Corder, Castagne, Rivet, Mormede, & Gaillard, 1992). Indeed, it is possible that hypoactive NPY function contributes both to adrenergic hyperreactivity and increased CRF activity in PTSD (Rasmusson & Friedman, 2002).

Dopamine

Amygdala activation by uncontrollable stress in laboratory animals produces activation of medial prefrontal cortex dopamine release but inhibition of release by the nucleus accumbens. This suggests that dopaminergic mechanisms play a role in the stress response that is both complicated and not well understood at this time (Charney, 2004). In the few published clinical studies with participants with PTSD, both urinary and plasma dopamine concentrations have been elevated (Hamner & Diamond, 1993; Lemieux & Coe, 1995; Yehuda et al., 1994).

Galanin

Galanin is a neuropeptide, found in 80% LC–NE noradrenergic neurons, that is released during activation. It reduces both LC and amygdala activation (Gentleman et al., 1989; Holmes & Crawley, 1995; Perez, Wynic, Steiner, &

Mufson, 2001). Like NPY, galanin appears to have anxiolytic effects and to antagonize the anxiogenic effects of stress when administered to rats (Bing, Moller, Engel, Soderpal, & Heilig, 1993; Charney, 2004; Moller, Sommer, Thorsell, & Heilig, 1999). Thus it appears that the net amount of stress-inducted anxiety will depend on how much NPY and galanin are available to offset the anxiogenic impact of norepinephrine. There are currently no studies on galanin with humans under stress or with PTSD, so this hypothesis has yet to be tested (Charney, 2004).

SEROTONERGIC SYSTEM

The serotonergic system has important reciprocal relationships with both the HPA and LC–NE systems. Excessive HPA activity associated with chronic life stress or PTSD produces down-regulation of 5-HT_{1A} receptors (which have anxiolytic effects) and upregulation of 5-HT_{2A} receptors (which are anxiogenic), resulting in abnormal neurotransmission in key limbic nuclei (Charney, 2004; McEwen, 1998; Southwick et al., 1999). There also may be synergistic interactions between $5HT_{1A}$ receptors and the GABA/benzodiazepine (GABA/BZ) system (Charney, 2004).

Clinical studies have shown that patients with PTSD exhibit a number of abnormalities associated with low 5-HT, such as impulsivity, rage, aggression, depression, panic, obsessional thoughts, and chemical dependency (Friedman, 1990).

The first two drugs to receive U.S. Federal Drug Administration approval as indicated treatments for PTSD are the selective serotonin reuptake inhibitor (SSRI) antidepressants sertraline and paroxetine. Among their other actions, SSRIs produce amelioration in all three symptom clusters of PTSD. Other antidepressants that affect serotonergic function, such as nefazadone and amitriptyline, have also shown efficacy in PTSD. Given the complexity of the serotonergic system with its large number of distinctive receptor types, it can be expected that in the future research will provide a better understanding of different roles played by the various serotonergic receptor systems in modulating the human stress response.

ENDOGENOUS OPIOIDS

CRF also activates the opioid peptide beta-endorphin, which reciprocally inhibits both the adrenergic and HPA components of the human stress response. The few studies on opioid activity in PTSD suggest that there may be both tonic and phasic abnormalities. Abnormal baseline opioid function has been detected among individuals with PTSD, although the specifics of such findings have varied from study to study. Elevated cerebrospinal fluid beta-endorphin levels were observed in male combat veterans with PTSD (Baker et al., 1997).

Studies on plasma beta-endorphin show mixed results: higher levels among Croatian women with PTSD due to the trauma of war (Sabioncello et al., 2000); normal levels in male combat veterans (Baker et al., 1997); and lower levels in a different cohort of combat veterans with PTSD (Hoffman, Watson, Wilson, & Montgomery, 1989). There is also evidence that exposure of people with PTSD to relevant trauma-related stimuli (e.g., Vietnam veterans with PTSD viewing combat scenes) produces an abrupt phasic elevation in circulating opioid levels (Pitman, van der Kolk, Orr, & Greenberg, 1990).

GLUTAMATERGIC SYSTEMS

Glutamate is an amino acid that is the brain's primary excitatory amino acid. It is rapidly mobilized during stressful or threatening situations and mediates almost all rapid excitatory transmission in the brain. Glutamatergic mechanisms are key to cognitive functions such as perception, appraisal, conditioning, extinction, and memory. Fear conditioning, sensitization, and resistance to extinction, all of which are mediated at *N*-methyl-D-aspartate (NMDA) synapses, are altered in PTSD (Charney, Deutch, Krystal, Southwick, & Davis, 1993) Information processing is disrupted with respect to learning and cognition. Memory function may be altered in the direction of excessive recall (e.g., intrusive recollections) or problems with retrieval (e.g., amnesia). Finally, dissociation, an abnormality that is beginning to be understood as a very important posttraumatic symptom, appears to represent a disruption of glutamatergic function (Chambers et al., 1999; Krystal, Bennett, Bremner, Southwick, & Charney, 1995). It appears likely that medication that normalizes neurotransmission at NMDA, non-NMDA, and metabotropic glutamate receptors may produce benefits for individuals with chronic PTSD.

GABA–BENZODIAZEPINE SYSTEM

In direct contrast to glutamate, gamma-aminobutyric acid (GABA) is the brain's major inhibitory neurotransmitter. The anxiolytic action of benzodiazepines is exerted primarily at $GABA_A$ receptors. A great deal of animal research shows that inescapable stress and anxiety are associated with reduced benzodiazepine receptor binding in the cortex and, possibly, the hippocampus (Weizman et al., 1989; Nutt & Malizia, 2001).

Human neuroimaging studies have shown reduced cortical and subcortical benzodiazepine receptor binding associated with PTSD and panic disorder (Bremner, Innis, White, et al., 2000; Bremner, Innis, Southwick, et al., 2000; Malizia et al., 1998). An important, unanswered question is whether such findings indicate a stress-induced down-regulation of benzodiazepine receptor binding or stress-induced alteration in GABA-ergic transmission that affects benzodiazepine receptor binding (Charney, 2004).

SUBSTANCE P

Based on their neuroanatomic distribution, it appears likely that substance P neurons are activated during the human stress response and have reciprocal interactions with the LC–NE system. Safe substance P antagonists have been synthesized and, in one randomized trial, the substance P antagonist MK-869 was as effective an antidepressant as the SSRI paroxetine (Kramer et al., 1998). Research with this class of medications certainly seems to offer possibilities for important clinical and conceptual advances in PTSD.

HYPOTHALAMIC–PITUITARY–THYROID AXIS

Thyroid-stimulating hormone (TSH) promotes thyroid gland secretion of thyroxine (T4), as well as conversion of T4 to the more metabolically active triiodothyronine (T3). Studies with combat veterans have demonstrated elevations in both T3 and T4. Such increases were positively associated with PTSD severity (Mason et al., 1995; Wang & Mason, 1999). Furthermore, unpublished observations on women with PTSD related to childhood sexual abuse (CSA), show higher T3 and lower TSH in comparison with female CSA survivors without PTSD (Friedman et al., 2001).

HYPOTHALAMIC–PITUITARY–GONADAL AXIS

Increased HPA activity suppresses all aspects of gonadal function, including secretion of gonadotropin-releasing hormone from the hypothalamus, follicle stimulating and luteinizing hormones from the pituitary, and estradiol and testosterone from the reproductive organs. There appears to be a direct hypothalamic–testicular pathway through which CRF suppresses testosterone secretion (Charney, 2004). Clinical studies in which testosterone was measured in people with PTSD have produced mixed findings. Elevated serum (Mason et al., 1990), unchanged serum (Bauer, Priebe, Graef, & Keurten, 1994), and reduced cerebrospinal fluid (Mulchahey et al., 2001) testosterone levels have been detected among male combat veterans with PTSD.

Estrogen may have an important role in the human stress response and may in part be responsible for the fact that PTSD prevalence is twice as great in women as in men (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Animal studies indicate that acute administration of estradiol reduces ACTH secretion and stress responsiveness. More prolonged estrogen treatment, however, enhances HPA activity (Charney, 2004; Stroud, Salovey, & Epel, 2002; Young, Altemus, Parkison, & Shastry, 2001). The mechanism of action of estrogen appears to be on CRF or ACTH secretion rather than directly on the adrenal cortex (Charney, 2004). Estrogen also has complex actions on serotonin activity (McEwen, 2002). Despite these intriguing findings, the role of estrogen in the development of PTSD awaits systematic scientific investigation.

GROWTH AXIS

Increased HPA activity interferes with growth axis function through inhibition of growth hormone release, as well as through suppression of growth at target tissues. Vietnam combat veterans with and without PTSD showed no difference in growth hormone levels (Laudenslager et al., 1998). Another study, in which PTSD was not measured, may be relevant. Sexually and physically abused boys (not assessed for PTSD) exhibited a blunted growth hormone response to both clonidine and levodopa, in contrast to nonabused control participants.

THE IMMUNE SYSTEM

Because blood levels of lymphocyte or natural killer (NK) cells vary according to the dynamics of catecholamine and glucocorticoid secretion, I limit this brief review to functional measures of immunological activity such as NK cytotoxicity per cell, assays of cell proliferation, and the cytokine response to specific antigens (Dhabhar & McEwen, 1997). More comprehensive reviews can be found elsewhere (see Dougall & Baum, 2004; Schnurr & Jankowski, 1999). The results in people with chronic PTSD are mixed. Extrapolating from findings associated with chronic stress syndrome (Chrousos, 1998; McEwen, 1998), one would expect to observe immunosuppression in individuals with chronic PTSD. Surprisingly, enhanced immunological function has actually been found more often than immunosuppression. Three studies on veterans with chronic PTSD observed higher cutaneous cell-mediated immunity and higher cytokine levels among those with PTSD, compared with a non-PTSD group (Burges-Watson, Muller, Jones, & Bradley, 1993; Laudenslager et al., 1998; Spivak et al., 1997). In a fourth report, however, immunological activation by antigens was no different among veterans with PTSD than among controls (Boscarino & Chang, 1999). Finally, Boscarino (1997) found that male Vietnam combat veterans with PTSD appeared to have reduced immunological function because they reported higher prevalence of non-sexually-transmitted infectious disease than non-PTSD veterans.

Given the complexity of the immune system and given that both tonic and phasic abnormalities have been found in people with PTSD in most biological systems investigated, one way to reconcile these diverse findings is to postulate that there is both a tonic state of immunosuppression and an episodic or phasic state characterized by enhanced immunological function.

PSYCHOBIOLOGICAL ASSESSMENT OF PTSD: A GAME PLAN FOR THE FUTURE

Table 14.1 summarizes all of the information presented thus far about psychobiological abnormalities associated with PTSD. There is no doubt that in the future many gaps in current knowledge will be filled, and many current controversies will be resolved. I wish to present here an overall strategy for assessing the functional capacity of the stress system in individuals. Application of such an approach need not wait until after someone has been exposed to a devastating traumatic event. As I have stated elsewhere, such an approach could be part of an overall health maintenance or preventive public health strategy through which a person's vulnerability to or resilience against traumatic stress might be evaluated in advance (Friedman, 2002).

Baseline Assessment

Such an approach would begin with a psychobiological assessment protocol that would focus on the primary components of the stress response rather than on downstream mechanisms. It might be a two-stage process measuring both baseline and elicited stress system measures. The first stage, analogous to a serum lipid profile for detecting individuals at greatest risk for heart disease, might consist of baseline serum or urinary indicators of HPA, LC–NE, serotonergic, opioid, and immunological function (see Table 14.2). Abnormal levels of any of these stress system components might identify those individuals most vulnerable (or resilient) to develop PTSD following traumatization.

As noted earlier, baseline measurement of almost any single biological marker, listed in Table 14.1, is unlikely to be very informative because it is liable to fall within the normal clinical range. A better strategy might be to consider some pattern of abnormalities that, taken together, give a better indication of the magnitude of allostatic load produced by PTSD. Returning to our serum lipid profile example, the cholesterol/high-density-lipoprotein (HDL) ratio is much more informative than either value alone. The possible utility of such an approach was recognized during the early days of PTSD biological research in which Mason, Giller, and colleagues (Mason, Giller, Kosten, & Harkness, 1988) suggested that the urinary norepinephrine/cortisol ratio might be a more useful indicator than either value by itself. Given the variability in urinary cortisol findings in more recent research, this no longer seems like a promising index. On the other hand, the DHEA/cortisol ratio or the norepinephrine/NPY + galanin ratio might prove to have clinical utility in the future.

Provocative Tests

Because the hallmark of PTSD is hyperreactivity, the second stage of stress system assessment might be a series of provocative tests to probe the functional capacity of the stress system itself. This would be analogous to a treadmill test to detect heart disease or a glucose tolerance test to detect diabetes mellitus in medical practice. Such provocative tests (shown in Table 14.2) might include (1) *in vivo* stress paradigms to assess mobilization of HPA, LC–NE, serotonergic, opioid, and immunological components of the stress response; (2) the dexamethasone suppression test to assess glucocorticoid receptor sensitivity; (3) yohimbine provocation to assess LC–NE function; (4) antigen provocation to assess humoral or cell-mediated immunity; or (5) other provocative tests. Should abnormalities be detected either at baseline or following provocation, the next question would be whether they can be corrected with pharmacological and/or behavioral treatment. Posttreatment assessment would subsequently determine whether the therapeutic intervention produced improvement in the psychobiological abnormalities previously detected (Friedman, 2002).

Thus I have outlined a systematic assessment strategy that utilizes psychobiological tools to determine the resilience or vulnerability of individuals to traumatic stress. It also detects the magnitude and characteristics of allostatic load borne by individuals who currently suffer from PTSD.

TABLE 14.2. A Psychobiological Assessment Strategy

Baseline assessment	HPA function:	CRF, ACTH, cortisol, DHEA, DHEA/cortisol ratio
	LC–NE function:	Norepinephrine, epinephrine, dopamine, NPY, galanin, norepinephrine/NPY + galanin ratio
	Other:	Serotonin, opioid, glutamatergic, GABA-ergic, substance P, thyroid, gonadal, and growth axis function
Provocative tests	*In vivo* stress paradigms to assess mobilization of:	HPA, LC–NE, other functions (per step 1)
	Dexamethasone suppression:	Glucocorticoid receptor sensitivity
	Yohimbine provocation:	LC–NE and NPY response
	Immunological provocation:	Humoral and cell-mediated immunity
Periodically repeat steps 1 and 2 for:		People exposed to traumatic stress
		People in high-risk professions
Treatment:	Correct abnormalities detected in steps 1, 2, or 3.	

Note. Adapted from Friedman (2002). Copyright 2002 by Elsevier Inc. Adapted by permission from Elsevier.
HPA, hypothalamic–pituitary–adrenocortical; CRF, corticotropin releasing factor; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandosterone; NPY, neuropeptide Y; GABA, gamma aminobutyric acid; LC–NE, locus ceruleus/norepinephrine.

Recent research with U.S. Special Forces military personnel provides a concrete example of this approach. Morgan and associates (Morgan et al., 2001; Morgan et al., 2000) monitored the stress response among military personnel exposed to an extremely stressful training experience at Fort Bragg, North Carolina. They showed that individuals who were best able to mobilize NPY tolerated the experience and performed better than those unable to achieve comparable NPY levels. These results suggest that stress-induced NPY mobilization may be an important index of resilience against PTSD. The clinical question raised by such findings is whether people with lower capacity to mobilize NPY under stressful circumstances might benefit from treatment with a (yet to be developed) medication that mobilizes NPY activity.

Indications for Repeated Psychobiological Assessment

There are a number of professions in which individuals are routinely exposed to potentially traumatic events in the course of their normal duties; these include soldiers, police, firefighters, emergency medical personnel, and disaster/refugee mental health clinicians. For such individuals, it would be appropriate to periodically repeat the baseline assessments and provocative tests (e.g., step 3 in Table 14.2). For the same reason that people at risk for heart disease have their serum lipid profiles repeated annually as part of routine health maintenance, people in these high-risk professions should have steps 1 and 2 repeated periodically, because they are at greater risk to develop PTSD. Furthermore, it might be advisable, as a matter of military policy, to repeat steps 1 and 2 following any major deployment to a war zone or for peacekeeping operations.

Assessment of Chronic PTSD

Whereas the emphasis in prevention and assessment of acutely traumatized individuals focuses exclusively on primary components of the human stress response (e.g., CRF, HPA, LC–NE, and probably immunological mechanisms), the focus in chronic PTSD may include downstream mechanisms. Such an assessment might also emphasize procedures to detect secondary neurotransmitter (e.g., 5-HT, dopamine, GABA-ergic, glutamatergic, substance P) or hormonal (e.g., thyroid, gonadotropic, growth hormone) abnormalities.

Assessment goals in chronic PTSD would be similar to laboratory assessment for any disorder. Step 1 and step 2 measurements would provide a clinical baseline against which any progress in treatment might be evaluated. Furthermore, such an approach would provide clinicians with a rational basis for choosing specific therapeutic targets and would enable them to choose a treatment strategy that focuses primarily on the HPA, LC–NE, serotonergic, or some other biological system that has been altered by the allostatic burden of PTSD.

SUMMARY

I began this brief chapter with a description of the human stress system as the context within which to understand neurotransmitter, neuropeptide, and neurohormonal alterations associated with PTSD. Then I reviewed the current empirical evidence concerning psychobiological abnormalities associated with PTSD. Finally, I proposed a conceptual approach to psychobiological assessment consisting of both baseline measurements and provocative tests. Because it appears that no single psychobiological alteration distinguishes PTSD from other psychiatric disorders, the current challenge is to search for a distinctive pattern of psychobiological abnormalities that sets PTSD apart from other disorders and to translate such laboratory findings into useful and feasible clinical diagnostic procedures.

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